In the Claims:

Please cancel claims 1-12, and 27, without prejudice. Applicants specifically preserve the right to pursue the currently canceled claims in one or more continuing applications.

Please amend claim 13 as follows:

13. (Amended) A chimeric polypeptide comprising [an OB protein] the amino acid sequence [capable of binding to a native OB receptor] of a native OB protein, with or without the initiating N-terminal methionine and with or without the native signal sequence, [linked] fused to an immunoglobulin heavy chain constant domain sequence.

Please amend claim 14 as follows:

14. (Amended) A chimeric polypeptide of claim 13 wherein said immunoglobulin constant domain sequence [is a constant domain sequence] comprises the hinge, CH2 and CH3 regions of an IgG.

Please amend claim 18 as follows:

18. (Amended) An isolated nucleic acid [sequence] molecule encoding [an OB protein-immunoglobulinfusion] a chimeric polypeptide comprising the amino acid sequence of a native OB protein, with or without the initiating N-terminal methionine and with or without the native signal sequence, fused to an immunoglobulin heavy chain constant domain sequence.

Please amend claim 21 as follows:

21. (Amended) A process comprising culturing the host cells of claim [16] 20 so as to express the nucleic acid encoding [an OB protein-immunoglobulin fusion] said chimeric polypeptide, and recovering said chimeric polypeptide.

Please amend claim 22 as follows:

22. (Amended) The process of claim 21 wherein said host cells are cotransformed with nucleic acid encoding at least two OB protein-immunoglobulin heavy chain constant domain fusions.

In claim 25, line 1, cancel "claim 20" and replace it with --claim 24--.

Please add the following new claim:

--28. The nucleic acid of claim 18 encoding a chimeric polypeptide comprising a mature native human OB polypeptide fused, at its C-terminus, to the N-terminus of an IgG constant domain sequence comprising the hinge, CH2 and CH3 regions.--

I.

Support for the Amendments

The foregoing amendments in the claims are supported at least in the paragraph bridging pages 4 and 5, and at page 9, lines 8-27. The amendments do not introduce new matter into the specification, therefore, their entry is respectfully requested.

II.

Formal Matters

Applicants were requested to make the title of the invention more descriptive. The foregoing amendment is believed to address this request.

Applicants were requested to correct the dependencies on claims 25 and 21, respectively. The foregoing amendments in the specification include these corrections.

III.

Double Patenting Rejections

Claims 1-27 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 13-23, 26, and 28-41 of copending application Serial No. 08/667,184. It is applicants intention to abandon copending application Serial No. 08/667,184 by failing to file a response to the pending Office Action mailed on April 29, 1998, and pursue the overlapping subject matter in the present application. Accordingly, the withdrawal of the present rejection is respectfully requested.

IV.

Objections and Rejections under 35 U.S.C. §112

Claims 7-9 were objected to as being "substantial duplicates" of claim 1. Without acquiescence in the Examiner's position, claims 7-9 have been canceled which moots their rejection.

Claim 21 was rejected under 35 U.S.C. §112, second paragraph, as being "indefinite." According to the rejection, this claim is "incomplete for failing to recite a recovery step", which ensures that the desired chimera is prepared. Claim 21 has been amended to include a recovery step, which should obviate the present rejection.

Claims 1-27 were rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for the nature form of the Ob protein and certain limited derivatives fused to Ig or PEG, does not reasonably provide enablement" for all long-half derivatives covered by these claims. Without acquiescence in this rejection, claims 1-12 and 27 have been canceled, and the remaining claims have been amended to cover chimeric polypeptides comprising native OB proteins, with or without the N-terminal initiating methionine and with or without the native signal sequence. As the Examiner has

acknowledged that the specification provides sufficient enablement for this subject matter, the withdrawal of the present rejection is respectfully requested.

Claims 1-3, 7-12 and 27 were rejected as being generic to a long half-life derivative of the OB protein, without reciting the make-up of the product. The cancellation of these claims, which was done without prejudice and without acquiescence in the Examiner's position, moots this rejection.

Claims 1-27 were rejected as non-enabled "for the full scope of the Ob protein that can be derivatized in order to have a product with the improved half-life." The Examiner acknowledged that applicants have shown that "the mature form of the Ob protein can be fused to the Ig or PEG and still maintain the activity of the protein", but found these results insufficient "to be reasonably predictive of the use of any Ob protein that will bind to the cognate receptor." As the claims have been amended to cover Ig fusions of certain well specified native OB proteins and derivatives, the present rejection is believed to be moot.

V.

Rejections Over Prior Art

Claims 1-3, 5-12 and 27 were rejected under 35 U.S.C. §103(a) as "being unpatentable over any one of Zhang et al., DiMarchi et al. or Basinski et al. in view of any one of Hakimi et al. ('356), Greenwalt et al. ('924), Haratani ('546), Nishimura et al. ('316), Davis et al. ('337), Yamasaki et al. (1988 or 1990) or Francis." The primary references were cited for their disclosure of mutant forms of the Ob polypeptide along with suggestions that such forms can be used to treat weight disorders. The secondary references were cited for their disclosure of making PEG conjugates of various polypeptides, not including OB proteins, to enhance their bioavailability. The Examiner concluded that "the skilled artisan would have been motivated by the combined teachings of both the primary and secondary reference for conjugating the Ob mutant of the primary to the various polymers of the secondary reference, and would

reasonably expected that such conjugation would have provided an additional benefit form use therapeutically."

As the claims rejected on this ground have been cancelled, the rejection is moot. It is emphasized, however, that the cancellation was done without acquiescence in the Examiner's position, and without prejudice. Applicants specifically retain the right to pursue the subject matter of the cancelled claims in one or more continuing applications.

Claims 1-3, and 7-27 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Zhang et al., Basinski et al. ('744 or '886), DiMarchi et al. ('954 or '336), in view of Shin et al. or Ashkenazi et al. The primary references were cited for their disclosure of human and murine Ob proteins and their mutant forms. The secondary references were relied upon for their disclosure of chimeric proteins including fusions of various mature proteins or polypeptides to immunoglobulins or their single chains, and of the advantages of such fusions. Neither the primary nor the secondary references disclose OB protein - Ig fusions. The Examiner represents, however, that such fusion proteins are prima facie obvious since they can be readily made by using the OB proteins taught in the primary reference in the fusions disclosed by the secondary references. In addition, the Examiner noted that prima facie obviousness is further supported by the teachings of the primary references for the potential benefits of using such protein, and also because of the broad and generic teaching of the secondary references that the disclosed conjugates can be made with different proteins.

Applicants vigorously traverse this rejection.

Applicants concede that native OB proteins were known in the art at the priority date of the present application. Similarly, it was known (as the secondary references attest) how to make receptor-immunoglobulinfusions (immunoadhesins), which were known to be useful, for example in therapy or as diagnostics. Indeed, the relevant art is clearly acknowledged in the Background Art section, and at pages 8-9 of the present application.

The specific OB protein-immunoglobulinchimeras of the present invention are believed to be patentable over the cited combination of references in view of their unexpected properties.

At the priority date of the present application, the receptor or receptors of the OB protein were unidentified. Researchers suggested, however, that at least one OB receptor, which was thought to be the biologically significant one, is localized in the brain.

Coleman, Diabetologica 14, 141-148 (1978) hypothesized that the ob receptor is encoded at the *db* locus of the hypothalamus. Campfield et al., Science 269, 546-49 (1995) reported experimental evidence that mouse OB protein can alter feeding behavior and energy balance when placed directly in the lateral ventricle of the brain of obese *ob/ob* and lean mice. The authors interpreted this finding to suggest that "one or more brain areas are among the target sites for mouse OB protein." They further suggested that the "identification of these brain areas will facilitate studies aimed at elucidating the neuronal pathways and networks and the underlying molecular mechanisms by which OB protein can influence feedings behavior and energy balance." (Page 548, concluding sentence.) Although the existence of peripheral receptors was not entirely ruled out, Maffei et al., Proc. Natl. Acad. Sci. 92, 6957-60 (1995) found that the expression of the ob gene in adipose tissue of mice with hypothalamic lesions did not result in a lean phenotype. They noted that the "most parsimonious explanation" of their data is that "the ob protein functions as an endocrine signaling molecule that is secreted by adipocytes and acts, directly or indirectly, on the hypothalamus." The authors added that "[d]irect effects on the hypothalamus would require that mechanisms exist to allow passage of the ob gene product across the blood-brain barrier. Mechanisms involving the circumventricular organ and/or specific transporters could permit brain access of a molecule the size of that encoded by the ob gene." (Page 6050, second column.)

The present inventors have found that chimeric polypeptides in which the OB protein is fused to an immunoglobulin constant domain sequence are effective in reducing body weight and adipose tissue depots. The present inventors have additionally found that such chimeric

polypeptides were significantly more potent than native human OB. These findings have been entirely unexpected against the background of the referenced prior art which suggested that the biologically relevant OB receptor is located in the brain. In view of their large molecular weight, the OB protein - Ig chimeras would not have been expected to be able to cross the blood-brain barrier, and therefore would have been expected biologically inactive. Hence, the finding of the present inventors that such chimeras are not only biologically active but more potent than the OB protein alone was entirely unexpected and is deserving patent protection.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present Amendment is accompanied by a Petition under 37 C.F.R. §1.48(b) requesting the deletion of Nancy Levin as an inventor. Dr. Levin was originally properly included as inventor, but due to claim amendments, her invention is no longer claimed in the present application.

The present application is now believed in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Respectfully submitted,
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Date: November 25, 1998

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